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Synthesis of 1-benzyloxypyrazin-2(1*H*)-one derivatives

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ABSTRACT

Different approaches for the synthesis of 1-benzyloxypyrazin-2(1*H*)-one derivatives from simple amino acids have been investigated. A library of 33 precursors for the preparation of *N*-hydroxy pyrazinones was obtained in moderate to good yields.

The pyrazinone is a valuable scaffold in medicinal chemistry. It is present amongst others in the inhibition of HCV NS3 protease,[1,2] neutrophil elastase,[3] prolyl oligopeptidase,[4] TF-FVIIa[5] and thrombin.[6,7] A lot of research in our group was directed towards the development of synthetic strategies for highly functionalized pyrazinones.[8–15] Since there are bioactive compounds known in nature containing an *N*-hydroxypyrazinone core (e.g., aspergillic acid, Fig. 1),[16–18] we focused our attention to the development of new strategies to synthesize pyrazinones containing 1-benzyloxy functionality. These compounds can potentially give rise to aspergillic acid-like hydroxamic acids upon deprotection. Furthermore, in extension of our work on 1-alkyl/aryl functionalized pyrazinone-3-carboxamides,[15] we also intended to prepare the corresponding 1-benzyloxy-3-carboxamide pyrazinones.

Our synthetic scheme for the synthesis of 1-benzyloxypyrazin-2(1*H*)-ones improves upon reported procedures[19–23] and is similar to chemistry we already applied in the preparation of 1-alkyl/aryl pyrazinones.[11,12] It relies on the base catalysed condensation of a glyoxal derivative with an amino acid hydroxamate. The condensations with phenyl glyoxal and diacetyl need a higher reaction temperature (50–70 °C) compared to those with glyoxal and methyl glyoxal. In order to avoid excessive side reactions resulting in very complex mixtures, it was important to use the glyoxal derivative as a limiting reagent (0.9 equiv, see Supplementary information) and to add it slowly to the reaction mixture via a syringe pump over the course of 30–120 min. The regioselectivity of this reaction with an unsymmetrical glyoxal derivative (methyl/phenyl glyoxal) was reported before[19,20] and was confirmed by us via NMR analysis. Proton H-6 in compounds **3b**,**c**,**e**,**f**,**m**,**n**,**q**,**t**,**w**,**y**,**zc**,**zg** (unsubstituted at position 6, but substituted at position 5) shows a clear NOE correlation with the methylene protons of the *O*-benzyl group, as well as an HMBC correlation with C-2 (Fig. 2).

The synthesis of 1-benzyloxy-3-alkylpyrazin-2(1*H*)-ones (**3a**–**f**, Scheme 1) was achieved by amidation of *N*-Boc protected amino acids **1** using *O*-benzyl hydroxylamine in combination with HOBt/EDCI/DIPEA/DMF, followed by Boc-deprotection and condensation. *O*-Benzyl hydroxamate **2a** could also be prepared via direct

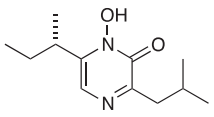

Figure 1. Aspergillic acid (**1**).

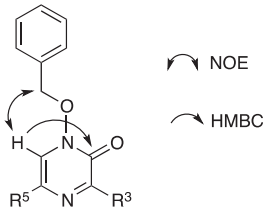

Figure 2. NOE and HMBC correlations of H-6 in compounds **3**.

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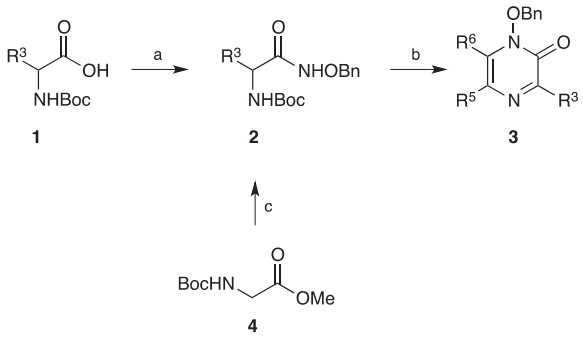


Compd.	R^3	R^5	R^6	Yield (%)
2a	H	-	-	86 (77, from **4**)
2b	Me	-	-	82
2c	*i*-Bu	-	-	80
3a	H	H	H	80 (28, ref. 22)
3b	H	Me	H	64 (53, ref. 23)
3c	H	Ph	H	62
3d	H	Me	Me	78 (53, ref. 21)
3e	Me	Me	H	52
3f	*i*-Bu	Ph	H	59

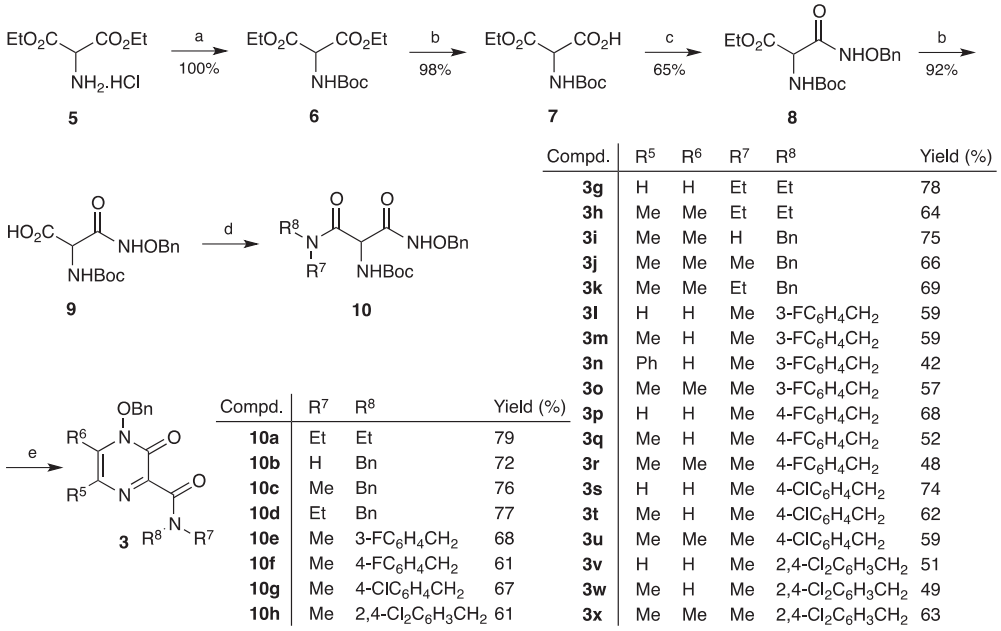
Scheme 1. Synthetic pathway for preparation of 1-benzyloxy-3-alkylpyrazin-2(1*H*)-ones. Reagents and conditions: (a) $BnONH_2$·HCl (1 equiv), HOBt (1.3 equiv), EDCI (1.3 equiv), DIPEA (2.3 equiv), DMF, −10 °C then rt, 16 h; (b) (i) 4 M HCl (10 equiv) in dioxane, rt, 30 min. (ii) $R^5R^6(CO)_2$ (0.9 equiv), 2 M NaOH, pH 8–10, MeOH–H_2O (2:1), −35 °C then rt, overnight; (c) $BnONH_2$ (1.1 equiv), LiHMDS (3.1 equiv), THF, −78 °C, 2 h.

amidation of the methyl ester of amino acid **4** using LiHMDS base in THF.[24] A slight reduction in yield and a shorter reaction time are observed in this instance (Scheme 1, entry **2a**). The direct amidation route could also be applied to more complex substrates as exemplified below in Scheme 3. Using this approach of slow addition with glyoxal as the limiting reagent, the previously reported 1-benzyloxypyrazin-2(1*H*)-ones **3a**, **3b** and **3d** were obtained in better yields as compared to the literature.[21–23]

The synthesis of the novel and more complex 1-benzyloxypyrazin-2(1*H*)-one 3-carboxamides **3g–zg** is described in Schemes 2 and 3. In this pathway, the amino group in diethyl amino malonate ester hydrochloride (**5**) is first Boc-protected to form **6**. This is followed by iterative mono-saponification amidation to generate **10** (Scheme 2). These compounds are then converted to pyrazine-2(1*H*)-ones **3g–zg** in moderate to good yields after Boc-removal (Schemes 2 and 3). Compounds **10** can alternatively directly be obtained via conversion of ethyl ester **11** using LiHMDS and NH_2OBn (Scheme 3). In the case of 3-carboxylated derivatives of 1-benzyloxypyrazin-2(1*H*)-one, the latter approach is able to reduce the number of reaction steps leading to the final products; however, it does limit the late stage diversification at C-3 of the target compounds, which in terms of library generation is a drawback.

In a further effort to shorten the synthetic protocol in the synthesis of 1-benzyloxypyrazin-2(1*H*)-ones **3**, we performed the cyclization of the product of Boc-deprotection of **8** with glyoxals to generate 1-benzyloxypyrazin-2(1*H*)-one 3-carboxyl ethyl esters **12**, which could be used as precursors in a one-step amidation to form **3** (Scheme 4) using $MgCl_2$ as Lewis acid catalyst.[25] The desired secondary amide products (**3zc**, **3zd** and **3zg**) could be obtained in high yields by treating ethyl esters **12** with primary amines. However, no conversion was detected in case of secondary amines even after prolonged reaction time and heating at a temperature of 50 °C (**3zh** and **3p** however can be synthesized via methods described in Schemes 2 and 3).

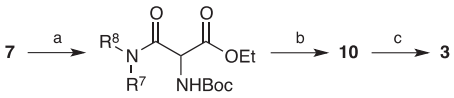
Using these approaches, a 33-component library of 1-benzyloxypyrazin-2(1*H*)-one derivatives, precursors for the synthesis of *N*-hydroxypyrazinones, has been prepared in moderate to good



Compd.	R^7	R^8	Yield (%)
10a	Et	Et	79
10b	H	Bn	72
10c	Me	Bn	76
10d	Et	Bn	77
10e	Me	3-$FC_6H_4CH_2$	68
10f	Me	4-$FC_6H_4CH_2$	61
10g	Me	4-$ClC_6H_4CH_2$	67
10h	Me	2,4-$Cl_2C_6H_3CH_2$	61

Compd.	R^5	R^6	R^7	R^8	Yield (%)
3g	H	H	Et	Et	78
3h	Me	Me	Et	Et	64
3i	Me	Me	H	Bn	75
3j	Me	Me	Me	Bn	66
3k	Me	Me	Et	Bn	69
3l	H	H	Me	3-$FC_6H_4CH_2$	59
3m	Me	H	Me	3-$FC_6H_4CH_2$	59
3n	Ph	H	Me	3-$FC_6H_4CH_2$	42
3o	Me	Me	Me	3-$FC_6H_4CH_2$	57
3p	H	H	Me	4-$FC_6H_4CH_2$	68
3q	Me	H	Me	4-$FC_6H_4CH_2$	52
3r	Me	Me	Me	4-$FC_6H_4CH_2$	48
3s	H	H	Me	4-$ClC_6H_4CH_2$	74
3t	Me	H	Me	4-$ClC_6H_4CH_2$	62
3u	Me	Me	Me	4-$ClC_6H_4CH_2$	59
3v	H	H	Me	2,4-$Cl_2C_6H_3CH_2$	51
3w	Me	H	Me	2,4-$Cl_2C_6H_3CH_2$	49
3x	Me	Me	Me	2,4-$Cl_2C_6H_3CH_2$	63

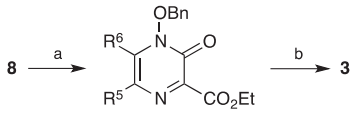
Scheme 2. Synthetic pathway for preparation of 1-benzyloxypyrazin-2(1*H*)-one 3-carboxamides **3**. Reagents and conditions: (a) Boc_2O (1.05 equiv), $NaHCO_3$ (1.05 equiv), DMAP (0.01 equiv), H_2O–dioxane, rt, overnight; (b) KOH (1 equiv), EtOH, rt, overnight; (c) $BnONH_2$·HCl (1 equiv), HOBt (1.3 equiv), EDCI (1.3 equiv), DIPEA (2.3 equiv), DMF, −10 °C then rt, 16 h; (d) R^7R^8NH (1 equiv), HOBt (1.3 equiv), EDCI (1.3 equiv), DIPEA (1.3 equiv), DMF, −10 °C then rt, 16 h; (e) (i) 4 M HCl (16 equiv) in dioxane, rt, 30 min; (ii) $R^5R^6(CO)_2$ (0.9 equiv), 2 M NaOH, pH 8–10, MeOH–H_2O (2:1), −35 °C then rt, overnight.



11

Compd.	R^5	R^6	R^7	R^8	Yield (%)
11a	-	-	Et	Et	84
11b	-	-	H	3-$FC_6H_4CH_2$	73
11c	-	-	H	4-$FC_6H_4CH_2$	80
11d	-	-	H	4-$ClC_6H_4CH_2$	69
11e	-	-	H	3,4-$Cl_2C_6H_3CH_2$	78
10a	-	-	Et	Et	79
10i	-	-	H	3-$FC_6H_4CH_2$	66
10j	-	-	H	4-$FC_6H_4CH_2$	64
10k	-	-	H	4-$ClC_6H_4CH_2$	57
10l	-	-	H	3,4-$Cl_2C_6H_3CH_2$	67
3y	Me	H	Et	Et	42
3z	H	H	H	3-$FC_6H_4CH_2$	51
3za	Me	Me	H	3-$FC_6H_4CH_2$	47
3zb	H	H	H	4-$FC_6H_4CH_2$	60
3zc	Me	H	H	4-$FC_6H_4CH_2$	58
3zd	H	H	H	4-$ClC_6H_4CH_2$	67
3ze	Me	Me	H	4-$ClC_6H_4CH_2$	42
3zf	H	H	H	3,4-$Cl_2C_6H_3CH_2$	61
3zg	Me	H	H	3,4-$Cl_2C_6H_3CH_2$	49

Scheme 3. Direct amidation of ethyl ester **11**. Reagents and conditions: (a) R^7R^8NH (1 equiv), HOBt (1.3 equiv), EDCI (1.3 equiv), DIPEA (1.3 equiv), DMF, −10 °C then rt, 16 h; (b) $BnONH_2$ (1.1 equiv), LiHMDS (4.1 equiv), THF, −78 °C, 2 h; (c) (i) 4 M HCl (16 equiv) in dioxane, rt, 30 min. (ii) $R^5R^6(CO)_2$ (0.9 equiv), 2 M NaOH, pH 8–10, MeOH–H_2O (2:1), −35 °C then rt, overnight.



12

Compd.	R^5	R^6	R^7	R^8	Yield (%)
12a	H	H	-	-	68
12b	Me	H	-	-	61
3zc	Me	H	H	4-$FC_6H_4CH_2$	95
3zd	H	H	H	4-$ClC_6H_4CH_2$	90
3zg	Me	H	H	3,4-$Cl_2C_6H_3CH_2$	90
3zh	H	H	Me	Bn	0[c]
3p	H	H	Me	4-$FC_6H_4CH_2$	0[c,d]

Scheme 4. Synthesis of **3** via amidation of ester **12**. Reagents and conditions: (a) (i) 4 M HCl (16 equiv) in dioxane, rt, 30 min. (ii) $R^5R^6(CO)_2$ (0.9 equiv), 2 M NaOH, pH 7–8, MeOH–H_2O (2:1), −35 °C then rt, overnight; (b) (i) $MgCl_2$ (2 equiv), THF, rt, 5 min. (ii) R^7R^8NH (2.5 equiv), rt, 16 h; (c) No conversion, **12a** was recovered (by LC–MS); (d) 38% yield of **3p** (from **8**, Scheme 2).

yields with minimal reaction steps. Pyrazin-2(1*H*)-ones **3c**, **3e**, **3f** and 27 other 3-carboxamide substituted analogues **3g**–**zg** are new compounds. Deprotection of this library will be subject of another paper.

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Supplementary data

Supplementary data (general procedures for synthesis and characterization of all compounds, copies of ^1H and ^{13}C NMR spectra of compounds **3** and **12**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.100. These data include MOL files and InChiKeys of the most important compounds described in this article.

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